Interstitial Lung Disease Associated With the Idiopathic Inflammatory Myopathies

What Progress Has Been Made in the Past 35 Years?

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Interstitial lung disease is commonly associated with the autoimmune inflammatory myopathies dermatomyositis and polymyositis and accounts for significant morbidity and mortality in these conditions. In the 35 years since the association between inflammatory myopathy and interstitial lung disease was initially described, there has been progress in diagnosing and treating this disorder. Nevertheless, there remains much about pathogenesis and therapeutics to be learned. This review examines the changes in the understanding of this complex condition, highlighting recent advances and areas deserving of further study. *CHEST 2010; 138(6):1464–1474*

Abbreviations: ASA = antisynthetase syndrome; CADM = clinically amyopathic dermatomyositis; CYC = cyclophosphamide; DLCO = diffusing capacity for carbon monoxide; DM = dermatomyositis; HRCT = high-resolution CT; IIM = idiopathic inflammatory myopathy; ILD = interstitial lung disease; MA-ILD = myositis-associated interstitial lung disease; MTX = methotrexate; NSIP = nonspecific interstitial pneumonia; PFT = pulmonary function testing; PM = polymyositis

The idiopathic inflammatory myopathies (IIMs) affect more than 60,000 individuals in the United States and an estimated 770,000 worldwide.[1] Although widely considered a disease confined to muscle, interstitial lung disease (ILD) remains one of the greatest contributors to morbidity and mortality in IIM, resulting in an estimated excess mortality of 40%.[2] Myositis-associated interstitial lung disease (MA-ILD) may occur in the context of virtually all of the IIIM and yet remains poorly understood. Since the first reviews and comprehensive descriptions nearly

35 years ago by Frazier and Miller[3] and Schwarz et al,[4] many case series and a few prospective studies have addressed the pathogenesis of, and therapy for, this condition. Despite these efforts, ILD is independently associated with a poor quality of life for patients with myositis even when the response to the myopathic, arthritic, and dermatologic manifestations is favorable.

This article reviews MA-ILD, focusing on progress made over the past 35 years, as well as highlighting existing gaps in the understanding of this disorder. This review focuses specifically on the lung disease associated with dermatomyositis (DM), polymyositis (PM), and amyopathic dermatomyositis (ADM) and considers pathogenesis and epidemiology, approach to diagnosis, as well as current and investigational treatment modalities. Myositis can also be associated with other connective tissue diseases; bacterial, viral, and parasitic infections; certain drugs; and malignancy; and is found in juvenile forms. Given the less frequent association of ILD with these conditions, they will not be addressed in this review. Through critical review and synthesis of the relevant literature, we aim to clarify what is currently known regarding MA-ILD and bring into focus what remains to be elucidated regarding this multifaceted condition.

Interstitial Lung Disease

ILD encompasses a diverse group of pulmonary disorders also known as diffuse parenchymal lung diseases.[5] These diseases are typically classified together because of unifying clinical, physiologic, pathologic, and roentgenographic manifestations.[6] Since its description in 1956 by Golden and Bronk[7] and an initial effort at classification by Liebow and Carrington in 1969,[8] a precise classification system for ILD has continued to evolve as new clinical, histopathologic, and radiographic information develops. Despite multiple causes for ILD, all culminate in a final common pathway resulting in compromise of the alveolar-capillary interface with subjective dyspnea, decreased exercise tolerance, restrictive physiology, and evidence of reticulation and honeycombing of the lung parenchyma on CT scanning of the thorax. It is estimated that ILD affects 200,000 to 500,000 people in the United States alone and accounts for 100,000 hospitalizations each year.[6] The annual mortality for all forms of ILD is estimated at 40,000 persons, comparable to that for breast cancer.

Idiopathic Inflammatory Myopathies

The IIMs, initially defined by Bohan and Peter (Table 1) in 1975,[9,10] encompass a group of disorders in which muscle is targeted in an inflammatory, autoimmune attack that generally leads to muscle weakness. For the purposes of this review, we will not consider the myopathies associated with bacterial, viral, and parasitic diseases; the more uncommon inflammatory myopathies, such as granulomatous myositis or eosinophilic myositis; or inclusion body myositis, as these entities are rarely associated with ILD. The subtypes of IIM relevant to the discussion of ILD include PM, DM, clinically amyopathic DM (CADM), and the antisynthetase syndrome.

The Intersection of ILD and IIM: MA-ILD

It is estimated that among patients diagnosed with PM/DM, 35% to 40% will be afflicted with ILD during the course of their illness, although there is variation in prevalence estimates in the literature and few large-scale cohort studies are available (Table 2).[11-19] Little is known about how MA-ILD affects specific populations, including women, minorities, and people of various ages. Overall, ILD is a major contributor to morbidity and mortality, and once pulmonary involvement is recognized in PM or DM the 5-year mortality ranges from 0 to 50% according to several small studies.[2,20] One longitudinal study of 27 patients with DM found pulmonary involvement to be the leading cause of death over a 10-year follow-up period.[21]

Pathogenesis

There is a great deal yet to be learned regarding the pathogenesis of ILD in the context of myositis. The leading hypothesis is that MA-ILD begins as a cellular inflammatory process that fails to appropriately terminate and progresses to a fibroproliferative condition[22] often unresponsive to traditional immunosuppressive therapies. This hypothesis is supported by the longitudinal analysis of several biopsy-proven cases.[4,23] However, the variable progression of MA-ILD over time lends support to the presence of heterogeneity in its pathogenesis. This variability has led to the examination of a number of other hypotheses regarding the etiology of lung involvement.

Viral Hypothesis of ILD Etiology

One hypothesis is that the inflammatory cascade of MA-ILD, resulting in both the pulmonary and nonpulmonary manifestations, is initiated by an unidentified viral infection, although the associations to date are weak. Many viruses, including coxsackie, influenza, echoviruses, HIV, and human T-cell leukemia virus, have a known tropism to muscle or have been associated with overt myositis.[24-28] In vitro and animal models also implicate encephalomyocarditis, adenovirus type 2, and the mumps virus as possible etiologic agents.[29-31] Although these viruses are associated with the development of myositis, there is no recognized association with the development of ILD in these patients.

The hepatitis C virus (HCV) has increased seropositivity in patients with DM and PM,[32] and PM alone is known to complicate up to 1% of hepatitis C cases.[33] Simultaneous pathologic appearance of hepatitis C and MA-ILD has been reported,[32,34-36] including the association of Jo-1-positive ILD in a patient with PM with HCV infection.[36] Cytomegalovirus has been associated with rapidly progressive ILD in patients receiving immunosuppressive therapy for DM.[37,38] It is not established whether this represents a de novo infection or reactivation of latent cytomegalovirus contributing to a more fulminant manifestation of already-present ILD.

Finally, parvovirus B19 is known to be associated with a number of autoimmune conditions[39,40] and has been shown to be causally related to the microvascular injury seen in patients with ILD.[41] To date no study has assessed a sufficiently large population of patients with MA-ILD to confirm this association.

1. Symmetric proximal muscle weakness determine by physical examination.
2. Elevation of serum skeletal muscle enzymes (particularly creatine kinase and aldolase), serum glutamate oxaloacetate, pyruvate transaminases, and lactate dehydrogenase.
3. The electromyographic triad of short, small, polyphasic motor unit potentials; fibrillations, positive sharp waves, and insertional irritability; and bizarre, high-frequency repetitive discharges.
4. Muscle biopsy specimen abnormalities of degeneration, regeneration, necrosis, phagocytosis, and interstitial mononuclear infiltrate.
5. Typical skin rash of dermatomyositis, including a heliotrope rash, Gottron sign, and Gottron papules.

Polymyositis is defined through these criteria as definite (all of criteria 1-4), probable (any three of criteria 1-4), or possible (any two of criteria 1-4). Dermatomyositis is defined as definite (5 plus any three of criteria 1-4), probable (5 plus any two of criteria 1-4), or possible (5 plus any one of criteria 1-4).

Cellular and Immunologic Hypotheses of ILD Etiology

A number of studies have focused on components of the cellular immune system in the induction of MA-ILD. In muscle biopsy specimens, CD8+ T cells are more closely associated with PM,[42] whereas B cells and CD4+ T cells are more commonly seen with DM and ILD.[43] A study evaluating BAL fluid from patients with MA-ILD demonstrated increased T-cell clones compared with healthy controls, suggesting a potential role for T cells in the development of MA-ILD.[44] Studies examining lung biopsy specimens demonstrate that, in contrast to normal lung tissue in which the number of lymphocytes is low, biopsies from patients with PM/DM have markedly elevated lymphocyte numbers.[45-47] These cells, specifically the CD8+ T cells, although diffusely distributed in both affected and normal tissue, were noted to be activated.[48] Elevated levels of these activated cells have also been demonstrated in 22 patients with MA-ILD, with a difference noted in CD8+ levels between steroid-responsive and steroid-unresponsive patients.[49]

Immunogenetics almost certainly plays a role in the development of MA-ILD with known HLA haplotype specificity in the development of both PM and DM as well as associated ILD.[50,51] Recently, specific HLA-DRB1 and tumor necrosis factor-α subtypes have been reported in patients with MA-ILD.[52] Furthermore, the HLA-DRB1*03-DQA1*05-DQB1*02 haplotype is associated with (52.3% disease vs 16.5% controls, OR = 5.5) expression of the ILD phenotype in both DM and PM when associated with a positive antisynthetase antibody.[53]

Humoral Immunity and the Causal Antibody Hypothesis

The identification of autoantibodies, whether specific to myositis or associated with other connective tissue diseases, has led to consideration of a humoral immune etiology: the antisynthetase syndrome (Table 3). The autoantibodies in MA-ILD, which target any one of several aminoacyl-transfer RNA synthetases, are collectively termed antisynthetase antibodies (ASA). Anti-Jo-1, directed against histidyl-tRNA synthetase, is the most common ASA[54,55] (Table 4)[56] and was initially reported in 1976 in a patient with PM and ILD.[57] The complete syndrome was defined in 1990 based on the retrospective analysis of 29 patients with myositis and ILD.[58]

ILD is often the dominant symptom in patients with antisynthetase syndrome and, if present, drives the prognosis and response to therapy. Up to 40% of all patients with myositis, regardless of their ILD status, will be positive for one of the ASAs.[59] Larger published case series suggest that > 75% of patients with ASAs will develop ILD.[14,60] A recent cohort study of 90 patients known to be Jo-1-positive demonstrated that 86% of subjects had CT scan evidence of ILD.[61] Patients with DM positive for an ASA are more likely to have ILD than patients with antibody-negative

Table 2—Prevalence of Interstitial Lung Disease in Polymyositis/Dermatomyositis/Clinically Amyopathic Dermatomyositis, 2002-2009

Study/Year	Mean Age, y	Sex Distribution	Ratio of Classifications of DM/PM/CADM	Patients with ILD, No. (%) (PM/DM/CADM)
Tani et al[11]/2007, N = 23	54	6 male, 17 female	9/14/0	17 (74) (5/12/0)
Ye et al[12]/2007, N = 145	47	47 male, 98 female	61/56/28	70 (48.3) (28/21/21)
Fathi et al[13]/2004, N = 17	58	6 male, 11 female	9/8/0	11 (64.7) (7/4/0)
Kang et al[14]/2005, N = 72	44	14 male, 58 female	22/44/6	29 (40.3) (6/18/5)
Chen et al[15]/2007, N = 51	44	19 male, 32 female	11/28/12	23 (41.4) (3/16/4)
Won Huh et al[16]/2007, N = 99	48	43 male, 56 female	…	33 (33.3)
Chen et al[17]/2009, N = 141	51	50 male, 91 female	69/71/1	30 (21.3) (11/19)
Marie et al[18]/2002, N = 156	52	58 male, 98 female	90/66/0	36 (23.1)
Selva-O'Callaghan et al[19]/2005, N = 60	47	19 male, 41 female	17/43/0	22 (36.7)
Totals: N = 764	49	262 male, 502 female	288/330/47	326 (37.4) (60/90/30)

CADM = clinically amyopathic dermatomyositis; DM = dermatomyositis; ILD = interstitial lung disease; PM = polymyositis.

Table 3—*Proposed Criteria for the Antisynthetase Syndrome*

Patient must have:
Positive serologic testing for an anti-tRNA synthetase autoantibody
Plus one or more of the following conditions:
Evidence of myositis by Bohan and Peter criteria
Evidence of ILD by ATS criteria
Evidence of arthritis by clinical examination, radiographic findings, or patient self-report
Unexplained, persistent fever
Raynaud phenomenon
Mechanic's hands

ATS = American Thoracic Society. See Table 2 for expansion of other abbreviation.

DM (94% vs 23%) and are more likely to require prolonged, higher doses of immunosuppressive agents.[62] A number of smaller studies have confirmed these associations.[15,19,59] Also notable is the fact that patients with ASA may present as an undifferentiated connective tissue disease (symptoms including arthralgias, myositis, or dermatologic manifestation without a definable pattern).[63]

Whether antisynthetase antibodies are causative of MA-ILD or simply a marker of disease remains to be elucidated. Animal studies in which mice were injected with murine Jo-1 antibodies demonstrate an increase in targeted B and T cells as well as a phenotype consistent with diffuse lung and muscle inflammation.[64] Evidence that disease activity in humans directly correlates with antisynthetase antibody titer levels provides further compelling but indirect evidence of their pathogenic nature.[65,66] There is also a growing body of literature suggesting the ability of the antisynthetase autoantibodies and their cleaved fragments, once released into the extracellular milieu, to serve as chemokines and cytokines directly responsible for the migration of mononuclear cells and immature dendritic cells and the resultant proinflammatory cascade.[67-70] Other work to date, indicating the near-complete absence of these antibodies in the general population combined with early data suggesting unique phenotypic, cellular, and immunologic variation associated with the different antibodies,[71,72] makes their role as a causative agent of disease possible.

Table 4—*Known Antisynthetase Antibodies*[56]

Antibody	Antigen (tRNA Synthetase)	Prevalence in IIM, %
Jo-1	Histidyl	25-30
PL-7	Threonyl	2-5
PL-12	Alanyl	2-5
EJ	Glycyl	1
OJ	Isoleucyl	1
KS	Asparaginyl	1
Zo	Phenylalanyl	1
Tyr	Tyrosyl	1

IIM = idiopathic inflammatory myopathy.

Signs and Symptoms

The majority of patients with MA-ILD will have symptoms common to all interstitial lung diseases, including cough, dyspnea on exertion, decreased exercise tolerance, and fatigue. Clubbing of the digits may be seen, although it is often not apparent early in the disease. Importantly, this is a syndrome with extreme variability in its main features: patients may present with myositis or dermatologic manifestations or lung disease in any combination simultaneously or sequentially. Although the myopathic manifestations of the IIMs often precede lung involvement, this is not always the case. In one series, 18% of patients ultimately diagnosed with MA-ILD had no muscle-related symptoms at the time of radiographic or physiologic confirmation of lung involvement.[13] The same study demonstrated that patients with myositis and no evidence of lung involvement had a similar frequency of pulmonary complaints, reinforcing that dyspnea and/or hypoxia in this population can be caused both by intrinsic lung disease and by respiratory muscle weakness. Treatment effects are equally variable. In our clinical experience, response to steroids or other medications may be limited to the myositis, the skin disease, or the pulmonary disease, and any of these features may become treatment unresponsive over time, independent of the others. This suggests that a high index of suspicion for ILD is imperative and a standardized diagnostic algorithm should be considered in this population. A number of skin and joint manifestations may also herald the antisynthetase syndrome. These include nonerosive arthritis, mechanic's hands, and Raynaud phenomenon (Fig 1).

Diagnosis

Based on the existing literature and our large single-center experience, we present a diagnostic algorithm for ILD. This algorithm can be considered for all patients with PM, DM, and ADM upon presentation (Fig 2).

Pulmonary Function Testing

Pulmonary function testing (PFT) is a readily reproducible, validated, and minimally invasive procedure[73,74] that can both uncover occult MA-ILD and assess the response to therapy over time. Patients typically demonstrate a restrictive pattern of disease (FVC or total lung capacity <80% of the predicted value for age and height) with a decrease in the diffusing capacity for carbon monoxide (D_{LCO}). Notably, an FVC <60% predicted at the time of diagnosis has been associated with a worse overall survival.[14] PFTs are useful for deciding whether lung disease is worsening despite
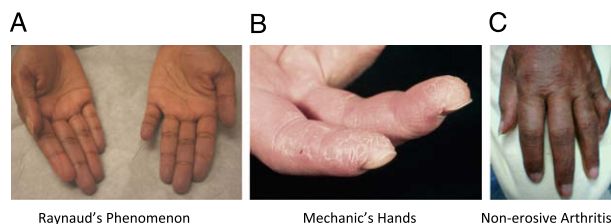
FIGURE 1. A, Raynaud phenomenon. B, Mechanic's hands. C, Nonerosive arthritis.

improving muscle and skin disease as well as determining the cause of common, nonspecific complaints, such as fatigue, which can have their basis in either lung or muscular dysfunction.

Complicating the use and interpretation of PFTs in this population is the potential coexistence of respiratory muscle weakness and ILD. As the disease manifesta-

tions can be variable both between individuals and in an individual over time, it is critical to interpret lung volumes with caution. A diagnosis of ILD in this population cannot be made in the absence of a confirmatory CT scan because PFTs with a restrictive physiology and low DLCO could be the result of respiratory muscle weakness alone. Similarly, progressive ILD can be obscured by a pseudostabilization of the PFTs as diaphragmatic strength improves. The use of the DLCO in these cases can be helpful as a relatively preserved DLCO in the setting of restrictive physiology favors respiratory muscle weakness. A reduced DLCO in this setting, however, is not as helpful as it could result from either ILD or atelectasis in the lung bases, which can accompany respiratory muscle weakness.

High-Resolution CT Scanning

High-resolution CT (HRCT) scanning of the thorax provides a sensitive marker of ILD with some potential to predict response to early therapy.[75,76] Characteristic HRCT findings include nodules, micronodules, linear opacities, irregularity of interfaces, ground glass opacities, fibrosis with or without honeycombing, consolidation, traction bronchiectasis, and bronchiolectasis.[13,77,78] Early studies in MA-ILD suggested a better response to therapy in patients with ground glass as the predominant pattern on CT scan.[79] In contrast, subsequent studies have suggested that patients demonstrating more ground glass opacities and reticulation were more likely to have a poor prognosis than those with a predominantly fibrotic pattern.[16,76] One study demonstrated a 72% vs 21.2% 3-year mortality based on the pattern of disease with ground glass/reticulation being worse.[16] Further research is needed to validate CT scanning as a prognostic tool.

Fiberoptic Bronchoscopy

Bronchoscopy with BAL can be helpful to rule out occult infections, which can resemble interstitial lung disease. This is especially relevant for patients on immunosuppressive drugs for a prolonged period of time because such patients are susceptible to atypical infections, including *Mycobacterium avium intracellulare*, *Pneumocystis* pneumonia, *Nocardia* lung disease, atypical bacterial pathogens, and, more rarely, cytomegalovirus and fungal infections.

The role of transbronchial biopsy in diagnosing the histologic type of ILD is limited. One recent study from Japan has shown a prognostic benefit to transbronchial biopsy in previously unclassified MA-ILD.[80] When biopsy specimens were grouped according to the type of intraluminal fibrosis observed (bud or polyp
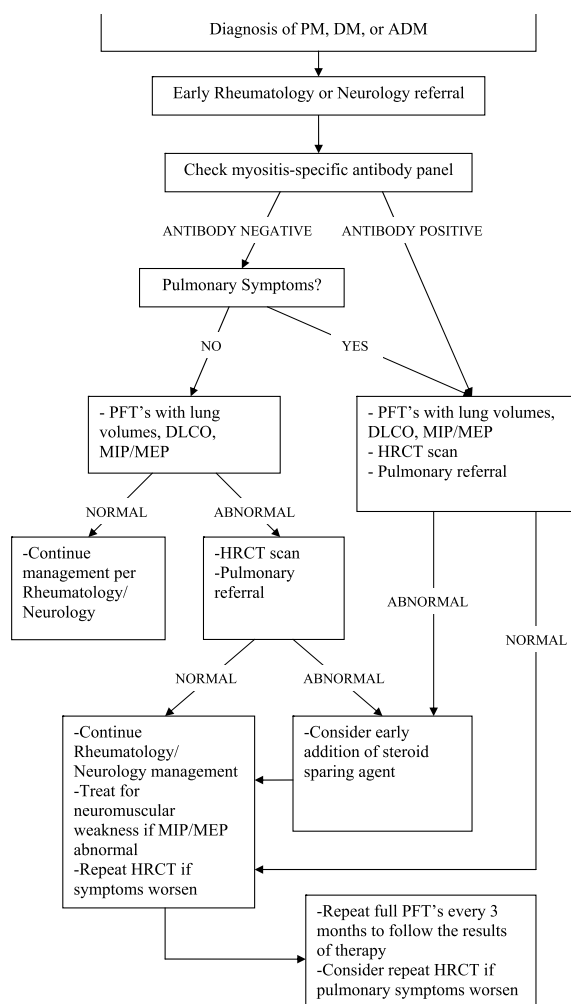

FIGURE 2. Myositis-associated interstitial lung disease diagnostic flow chart. ADM = amyopathic dermatomyositis; DLCO = diffusing capacity for carbon monoxide; DM = dermatomyositis; HRCT = high-resolution CT; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; PFT = pulmonary function test; PM = polymyositis.

type vs mural incorporation type), the patients with bud-type fibrosis had a 100% response rate to steroids, whereas the patients with mural incorporation-type fibrosis only responded 21% of the time and had a 5-year mortality of 29%.[80] At present, surgical lung biopsy remains the method of choice for diagnosis of ILD subclasses in patients with myositis.

Surgical Biopsy

The role of surgical biopsy remains controversial. Regional histopathologic variability can make representative tissue sampling challenging. This has lead to differing opinions in the literature regarding whether biopsy findings are sufficient to guide treatment or aid in prognosis. Numerous small studies have reported MA-ILD histology, and the results are summarized in Table 5.[81,82]

The majority (56.3%) of reported patients have nonspecific interstitial pneumonia (NSIP) as their biopsy diagnosis, with usual interstitial pneumonia (17.5%), cryptogenic organizing pneumonia (14.6%), diffuse alveolar damage (5.8%), lymphocytic interstitial pneumonia (3.8%), and unknown histology (1.9%) following in decreasing frequency. Although one series identified a relationship between biopsy subtype and disease prognosis,[47] 5-year mortality appears to have little relationship to biopsy subtype in three other studies[2,81,82] and offers unclear prognostic value above CT scanning and pulmonary function testing alone. At this time, the evidence suggests that open lung or video-assisted thoracoscopic surgery biopsy should be used only to clarify the diagnosis of ILD if there is clinical uncertainty. Given the paucity of literature, the role of surgical lung biopsy in prognosis and therapeutic decision making is an area deserving of further research.

Serum Biomarkers

The serum muscle enzyme creatine kinase has been examined as a biomarker of IIM disease activity, but its role in MA-ILD has not been studied to date.

Other general markers of inflammation, such as the erythrocyte sedimentation rate[83] and lactate dehydrogenase,[83] have been shown to be elevated in MA-ILD in a single case study. More promising is the mucin-like glycoprotein KL-6, whose elevation in MA-ILD has been demonstrated in several small, prospective studies in Europe and Japan.[84-86] Other serum biomarkers have also been described in a limited fashion, including B-cell activating factor,[87] surfactant protein D,[86] and the tandem of cancer-associated serum antigen and CA 15-3.[88,89] The level of current evidence favors more lung-specific measures, such as PFTs and HRCT scanning, in following the pulmonary disease course.

Current Therapeutic Approaches

Despite the common use of steroids and various steroid-sparing agents, no prospectively tested therapeutic regimen for MA-ILD exists at this time. Since the recognition of MA-ILD, corticosteroids, either in oral or IV form, have been regarded as the mainstay of therapy. A number of immune modulating agents have been tested in small studies. The options for therapy are presented below, but it should be noted that the majority of the studies were neither placebo-controlled nor prospective.

In addition to more commonly accepted medications, a number of other experimental therapeutic agents and approaches have been tried in an effort to slow the progression of MA-ILD. Among these are immunosuppressive and biologic agents targeted at disrupting T- and B-cell function directly. Less conventional and potential future therapeutic interventions are addressed in Table 6.[90-104]

Corticosteroids

Empirical treatment of MA-ILD with oral corticosteroids dates to the initial reports of this condition.[3,4] Although the de facto standard of care (historically and currently) for MA-ILD, corticosteroids have little prospective evidence supporting their use. In

Table 5—Lung Biopsy Results of Patients With Myositis-Associated Interstitial Lung Disease

Study/Year	NSIP[a]	UIP	COP	DAD	LIP	Unclassified
Fujisawa et al[80]/2005, N = 10	7	3	0	0	0	0
Cottin et al[2]/2003, N = 17	11	2	2	0	1	1
Tansey et al[81]/2004, N = 13	7	1	5	0	0	0
Shi et al[77]/2008, N = 26	14	1	4	5	2	0
Fathi et al[13]/2004, N = 11	4	5	2	0	0	0
Won Huh et al[16]/2007, N = 9	4	4	0	1	0	0
Totals: N = 86	47	16	13	6	3	1

Where results were listed as minor pattern vs major pattern, only major patterns are reported. COP = cryptogenic organizing pneumonia; DAD = diffuse alveolar damage; LIP = lymphocytic interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.
[a]In studies where results were reported as cellular vs fibrotic NSIP, results were combined into the NSIP category.

these articles and other smaller case series,[105] roughly 50% of patients with PM/DM initially responded to corticosteroid therapy alone. Existing literature derived from small case series of patients analyzed retrospectively for relatively short periods of time without a standard dosing schedule or consistent definition of response show that the effect of corticosteroids in MA-ILD was variable.[47,106-108] Later studies have confirmed these mixed results.[109] Corticosteroids remain the standard of care, making future placebo-controlled prospective studies difficult. This lack of evidence should be recognized when treating patients in the clinical setting.

Azathioprine

Through its prevention of lymphocyte clonal expansion and the resultant effects on both cellular and humoral immunity, azathioprine has proved useful in treating a number of autoimmune conditions. In our clinical experience and according to the literature, azathioprine is the most common clinically used corticosteroid-sparing agent in the treatment of MA-ILD.[110] Only one case report of azathioprine as a successful adjunctive maintenance therapy for the control of MA-ILD could be found.[111] No prospective trials or large case series exist.

Methotrexate

Methotrexate (MTX) is an inhibitor of folic acid metabolism as well as purine metabolism and T-cell activation.[96] Its successful use in treating the arthritis and myositis of PM/DM as an adjunctive agent when steroids have failed[112,113] is well established. No trials of MTX specifically for MA-ILD exist. Despite the absence of pulmonary-specific evidence and due to its relatively low side-effect profile, MTX has become accepted in the treatment of MA-ILD. Particular care must be taken in treating MA-ILD with MTX given the agent's known association with idiosyncratic drug-related hypersensitivity pneumonitis.[114] Using literature from rheumatoid arthritis cohorts, it can be estimated to affect approximately 0.5% of those who take the drug,[115] with another review further classifying the risk as one event per 35.4 patient-years of therapy.[116] In the rheumatoid arthritis population, it has been suggested that pneumonitis is more common in patients who are diabetic, have hypoalbuminemia, or are > 60 years of age, or, notably, in those in whom preexisting lung disease was noted.[117] When this occurs, often early in the course of therapy,[116] it can be difficult to distinguish symptoms as being related to the drug (using the major and minor criteria developed by Searles and McKendry)[118] or a manifestation of the MA-ILD itself without a lung biopsy to obtain histopathology. Both the drug toxicity and a worsening of the ILD can present with interstitial infiltrates, increased dyspnea or cough, and a decline in pulmonary function, including a drop in the DLCO. Given this diagnostic dilemma, stopping the drug and switching immunomodulatory agents is prudent should pulmonary symptoms, PFT results, or CT scan findings worsen after starting this agent.

Cyclophosphamide

Cyclophosphamide (CYC), commonly used in rapidly progressive MA-ILD, is believed to exert its immunosuppressive actions through a variety of effects on T cells resulting in abolished immunologic memory.[119] Because of its side-effect profile as an alkylating agent, its use is commonly restricted to refractory, treatment-resistant MA-ILD. It can be administered orally or IV (monthly IV pulse), most commonly with corticosteroids. Several case studies demonstrate its potential efficacy in treating MA-ILD.[120-123] Only one study showed improvement as an adjunct to corticosteroids when CYC was administered orally.[111] One larger case series of CYC in pulse-dose fashion (300-800 mg/m² approximately every 5 days for 4 weeks) in combination with corticosteroids in 17 refractory patients[124] noted significant

Table 6—Less Conventional/Potential Future Therapeutic Approaches

Agent	Class	Level of Evidence/Demonstration of Benefit	Potential Concerns
Cyclosporin A (CsA)	Calcineurin inhibitor	Several case reports,[90-93] one retrospective trial,[80] one prospective trial[94]	Nephrotoxicity, hepatotoxicity, infection
Tacrolimus (FK-506)	Calcineurin inhibitor	One case report,[95] several retrospective reviews[94,96-98]	Nephrotoxicity, weakness, infection, induction of neoplasm
Mycophenolate mofetil (MMF)	Inhibitor of purine synthesis	Two small retrospective reviews[99,100]	Bone marrow suppression, infection
Leflunomide	DMARD	Single case report[101]	Hepatotoxicity, bone marrow suppression
IV immunoglobulin (IVIg)	Pooled IgG immunoglobulins	Single case report,[102] single retrospective trial[103]	Aseptic meningitis, nephrotoxicity, anaphylaxis
Autologous stem cell transplantation	N/A	Single case report[104]	Extremely invasive, high risk of infection

DMARD = disease-modifying antirheumatic drug; N/A = not applicable.

improvement in dyspnea, vital capacity, and HRCT scan findings (although two Jo-1-positive patients had ILD flares). Another prospective, randomized trial of CYC demonstrated efficacy over corticosteroids alone when used in combination with prednisolone and cyclosporine A.[125] In this trial, 10 patients with DM and acute/subacute interstitial pneumonitis were initially treated with the combination therapy. When compared with historical controls treated with corticosteroids alone, the study group had a lower, although significant, mortality (50% vs 75%) over 3 months.

Conclusion

Since the original reviews describing myositis-associated interstitial lung disease in the mid-1970s, much has changed in the way we view and approach this condition. As case series and cohort studies grow in number, multiple disciplines are contributing to advances in the science of this disease. With this growing body of literature, we are poised to make larger advances in the coming years. Although its effect on morbidity and mortality of those affected, as well as its cost to the health system, have become clearer, much remains to be done in terms of understanding the cause of MA-ILD. The discoveries of antisynthetase autoantibodies and HLA subtype associations provide encouragement that a more accurate classification and predictive system may be on the horizon.

To date, as has been the case for >35 years, the mainstay of treatment of MA-ILD is corticosteroids. New therapies, including the use of targeted immune modulators as well as the more experimental methods described in this review, require further prospective, large-scale study, specifically in patients with myositis demonstrating ILD, but offer a promise of less toxic, more tailored therapy.

In order to address this relatively rare condition, multicenter, multinational, collaborative efforts spanning the numerous disciplines involved in the treatment of patients with MA-ILD are required. The development of large, open-access patient databases will facilitate understanding of this disease and help drive progress in the accurate diagnosis and treatment of MA-ILD.

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